Progynova 2 mg tablets

1. Name of the medicinal product 药品名称

Progynova ® 2 mg Tablets Progynova® 2 毫克片剂

2. Qualitative and quantitative composition 定性和定量组成

Each memo pack contains 28 tablets each containing estradiol valerate 2.0 mg. 每个便携纸盒含 28 片，每片含有 2.0 毫克戊酸雌二醇。

Excipients with known effect已知作用的辅料

Lactose monohydrate and sucrose 单水乳糖合物和蔗糖

For the full list of excipients, see section 6.1. 有关辅料的完整列表，请参阅第 6.1 节。

3. Pharmaceutical form 药剂形式

White sugar coated tablet for oral administration. 用于口服给药的白糖衣片剂。

4. Clinical particulars 临床资料

4.1 Therapeutic indications 适应症

Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in peri- and postmenopausal women. 激素替代疗法 (HRT) 用于治疗围绝经期和绝经后妇女的雌激素缺乏症状。

Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis. 预防绝经后妇女的骨质疏松症，这些妇女对未来骨折的高风险不耐受或禁忌使用其他批准用于预防骨质疏松症的药物。

See also Section 4.4. 另见第 4.4 节。

4.2 Posology and method of administration 药理学和给药方法

• Posology • 药理学

Progynova is an oestrogen-only product. Progynova 是一种仅含雌激素的产品。

One tablet of Progynova 2 mg to be taken daily. It does not matter at what time of day the woman takes her tablet, but once she has selected a particular time she should keep to it every day. Treatment is continuous, which means that the next pack follows immediately without a break. 每天服用一粒 Progynova 2 mg。女性在一天中的什么时间服用药并不重要，但一旦她选择了特定的时间，她就应该每天坚持下去。治疗是连续的，这意味着下一步会立即进行而不会中断。

For initiation and continuation of treatment of menopausal symptoms, the lowest effective dose for the shortest duration (see also section 4.4) should be used. Treatment to control menopausal symptoms should be initiated with Progynova 1 mg. If considered necessary,

Progynova 2 mg should be used. Once treatment is established the lowest effective dose necessary for relief of symptoms should be used. 对于更年期症状的开始和继续治疗，应使用最短持续时间的最低有效剂量（另见第 4.4 节）。应以 Progynova 1 mg 开始治疗以控制更年期症状。如果认为有必要，应使用 Progynova 2 mg。一旦开始治疗，应使用缓解症状所需的最低有效剂量。

For prevention of postmenopausal osteoporosis one tablet of Progynova 2 mg is to be taken daily. 为预防绝经后骨质疏松症，每天服用 1 片 Progynova 2 mg。

In women with an intact uterus, a progestogen should be added to Progynova for at least 12 - 14 days each month/28 day cycle. Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestogen in hysterectomised women. 对于子宫完整的女性，应在 Progynova 中添加孕激素，每个月至少 12 - 14 天/28 天周期。除非先前诊断为子宫内膜异位症，否则不建议在子宫切除的女性中添加孕激素。

• How to start Progynova 2 mg • 如何开始服用 Progynova 2 mg

If the woman has an intact uterus and is still menstruating, a combination regimen with Progynova and a progestogen, commencing with the oestrogen phase, should begin on the first day of bleeding. If the menstrual periods are very infrequent or if amenorrhoea is established, she may start at any time provided, if appropriate, pregnancy has been excluded (see section 4.6). 如果女性子宫完整且仍在月经期，则应在出血的第一天开始使用 Progynova 和孕激素的组合方案，从雌激素阶段开始。如果月经周期非常少或如果确定闭经，她可以在任何时候开始，前提是在适当的情况下已排除怀孕（见第 4.6 节）。

In women transferring from a continuous combined HRT product, treatment with Progynova may be started on any day. 在从连续 HRT 产品转移的女性中，可以在任何一天开始使用 Progynova 治疗。

In women transferring from cyclic or continuous sequential HRT regimens, the woman should complete the cycle and then change to Progynova without a break in therapy. 在从循环或连贯 HRT 方案转移的女性中，女性应完成周期，然后在不中断治疗的情况下更换为 Progynova。

• Missed or lost tablets • 错过或失药

If the woman forgets to take a tablet at the usual time, she may take it within the following 12 hours. If the woman is more than 12 hours late the forgotten tablet should not be taken and the remaining tablets taken at the usual time on the right days. A missed dose may lead to breakthrough bleeding or spotting. 如果女性忘记在平时服用药片，她可能会在接下来的 12 小时内服用。如果女性迟到超过 12 小时，则不应服用忘记的药片，其余药片应在正确日期的通常时间服用。漏服可能会导致穿透性出血或血斑。

Paediatric population 儿科人群

Not recommended for children 不建议儿童使用

Method of administration 给药方法

The tablets can be taken with or without food. The tablets should be swallowed whole with a glass of water or milk. The tablets should be taken at the same time each day. 片剂可以在有或没有食物的情况下服用。片剂应与一杯水或牛奶一起吞服。药片应每天在同一时间服用。

4.3 Contraindications 禁忌症

- Known, past or suspected breast cancer - 已知、既往或疑似乳腺癌

- Known or suspected oestrogen-dependent malignant tumours e.g. endometrial cancer - 已知或疑似雌激素依赖性恶性肿瘤，例如：子宫内膜癌

- Undiagnosed genital bleeding - 未确诊的生殖器出血

- Untreated endometrial hyperplasia - 未经治疗的子宫内膜增生

- Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism) - 既往特发性或当前静脉血栓栓塞（深静脉血栓形成、肺栓塞）

- Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency, see section 4.4) - 已知的易血栓性疾病（例如蛋白 C、蛋白 S 或抗凝血酶缺乏症，见第 4.4 节）

- Active or recent arterial thromboembolic disease e.g. angina, myocardial infarction - -活动性或近期动脉血栓栓塞性疾病，如心绞痛、心肌梗塞

- Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal -急性肝病，或有肝功能检查不能恢复正常的肝病史

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1 - 对活性物质或第 6.1 节中列出的任何辅料过敏

- Porphyria - 卟啉症

4.4 Special warnings and precautions for use 特别警告和使用注意事项

• For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risk and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk. • 对于绝经后症状的治疗，HRT 应仅针对对生活质量有不利影响的症状开始。在所有情况下，应至少每年对风险和收益进行仔细评估，并且只有在收益大于风险时才应继续使用 HRT。

• Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favourable than in older women. • 关于 HRT 治疗过早绝经的风险的证据有限。然而，由于年轻女性的绝对风险水平较低，这些女性的利益和风险的平衡可能比老年女性更有利。

Medical examination/follow-up: 体检/随访：

• Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse (see 'Breast cancer' below). Investigations, including appropriate imaging tools, e.g mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual. • 在开始或重新开始 HRT 之前，应采集完整的个人和家庭病史。体格检查（包括盆腔和乳房）应以此为指导以及使用禁忌症和警告。在治疗期间，建议根据女性个体的频率和性质进行定期检查。应告知女性应向医生或护士报告乳房的哪些变化（参见下文'乳腺癌'）。调查，包括适当的成像工具，例如乳房 X 光检查，应根据当前接受的筛查实践进行，并根据个人的临床需要进行修改。

Conditions which need supervision: 需要监督的条件：

• If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with Progynova, in particular: • 如果存在以下任何一种情况，以前发生过，和/或在怀孕或以前的激素治疗期间加重，应密切监督患者。应该考虑到这些情况在使用 Progynova 治疗期间可能会复发或加重，特别是：

- Leiomyoma (uterine fibroids) or endometriosis- 平滑肌瘤（子宫肌瘤）或子宫内膜异位症

- Risk factors for, thromboembolic disorders (see below) - 血栓栓塞性疾病的危险因素（见下文）

- Risk factors for oestrogen dependent tumours, e.g. 1st degree heredity for breast cancer - 雌激素依赖性肿瘤的危险因素，例如乳腺癌一级遗传

- Hypertension - 高血压

- Liver disorders (e.g. liver adenoma) - 肝脏疾病（例如肝腺瘤）

- Diabetes mellitus with or without vascular involvement - 伴有或不伴有血管受累的糖尿病

- Cholelithiasis - 胆石症

- Migraine or (severe) headache - 偏头痛或（严重）头痛

- Systemic lupus erythematosus - 系统性红斑狼疮

- A history of endometrial hyperplasia (see below) - 子宫内膜增生病史（见下文）

- Epilepsy - 癫痫

- Asthma - 哮喘

- Otosclerosis - 耳硬化症

- Hereditary angioedema. - 遗传性血管性水肿。

Reasons for immediate withdrawal of therapy: 立即停止治疗的原因：

Therapy should be discontinued in case a contraindication is discovered and in the following situations: 如果发现禁忌症和以下情况，应停止治疗：

- Jaundice or deterioration in liver function - 黄疸或肝功能恶化

- Significant increase in blood pressure - 血压显着升高

- New onset of migraine-type headache - 新发偏头痛型头痛

- Pregnancy. - 怀孕。

Endometrial hyperplasia and carcinoma 子宫内膜增生和癌

• In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among oestrogen-only users varies from 2- to 12-fold greater compared with non-users, depending on the duration of treatment and oestrogen dose (see Section 4.8). After stopping treatment risk may remain elevated for at least 10 years. • 在子宫完整的女性中，长期单独使用雌激素会增加子宫内膜增生和癌变的风险。据报道，仅雌激素使用者的子宫内膜癌风险比非使用者高 2 至 12 倍，具体取决于治疗持续时间和雌激素剂量（见第 4.8 节）。停止治疗后，风险可能会持续升高至少 10 年。

• The addition of a progestogen cyclically for at least 12 days per month/28 day cycle or continuous combined oestrogen-progestogen therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-only HRT. • 在未切除子宫的女性中，至少每月 12 天/28 天周期循环添加孕激素或连续联合雌激素-孕激素治疗可防止与仅使用雌激素 HRT 相关的过度风险。

• For oral doses of estradiol > 2mg, conjugated equine oestrogens > 0.625 mg and patches > 50 micrograms/day the endometrial safety of added progestogens has not been demonstrated. • 对于口服剂量> 2mg 的雌二醇、> 0.625 mg 的结合马雌激素和> 50 微克/天的贴剂，添加孕激素的子宫内膜安全性尚未得到证实。

• Break-through bleeding and spotting may occur during the first months of treatment. If break-through bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy. • 治疗的最初几个月可能会出现穿透性出血和血斑。如果在治疗一段时间后出现穿透性出血或血斑，或在停止治疗后继续出现，则应调查原因，可能包括子宫内膜活检以排除子宫内膜恶性肿瘤。

• Unopposed oestrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of progestogens to oestrogen replacement therapy should be considered in women who have undergone hysterectomy because of endometriosis, if they are known to have residual endometriosis. • 无对抗的雌激素刺激可能导致子宫内膜异位症残留病灶发生癌前病变或恶变。因此，对于因子宫内膜异位

症而接受子宫切除术的女性，如果已知有残留的子宫内膜异位症，则应考虑在雌激素替代疗法中添加孕激素。

Breast cancer乳腺癌

The overall evidence shows an increased risk of breast cancer in women taking combined oestrogen-progestogen or oestrogen-only HRT, that is dependent on the duration of taking HRT. 总体证据表明，服用雌激素 - 孕激素或仅雌激素 HRT 的女性患乳腺癌的风险增加，这取决于服用 HRT 的持续时间。

Combined oestrogen-progestogen therapy雌孕激素联合治疗

• The randomised placebo-controlled trial the Women's Health Initiative study (WHI), and a meta-analysis of prospective epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined oestrogen-progestogen for HRT that becomes apparent after about 3 (1-4) years (see Section 4.8). • 妇女健康倡议研究 (WHI) 的随机安慰剂对照试验和前瞻性流行病学研究的荟萃分析一致发现，服用雌激素-孕激素联合进行 HRT 的妇女患乳腺癌的风险在大约 3 分钟后变得明显。 (1-4) 年（见第 4.8 节）。

Oestrogen-only therapy仅雌激素治疗

• The WHI trial found no increase in the risk of breast cancer in hysterectomised women using oestrogen-only HRT. Observational studies have mostly reported a small increase in risk of having breast cancer diagnosed that is lower than that found in users of oestrogen-progestogen combinations (see Section 4.8). • WHI 试验发现仅使用雌激素 HRT 的子宫切除妇女患乳腺癌的风险没有增加。观察性研究大多报告诊断出乳腺癌的风险略有增加，低于雌激素-孕激素组合使用者的风险（见第 4.8 节）。

• Results from a large meta-analysis showed that after stopping treatment, the excess risk will decrease with time and the time needed to return to baseline depends on the duration of prior HRT use. When HRT was taken for more than 5 years, the risk may persist for 10 years or more. • 一项大型荟萃分析的结果表明，停止治疗后，过度风险会随着时间的推移而降低，恢复到基线所需的时间取决于先前使用 HRT 的持续时间。当 HRT 服用超过 5 年时，风险可能会持续 10 年或更长时间。

• HRT, especially oestrogen-progestogen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer. • HRT，尤其是雌激素-孕激素联合治疗，增加了乳腺 X 线图像的密度，这可能对乳腺癌的放射学检测产生不利影响。

Ovarian cancer 卵巢癌

• Ovarian cancer is much rarer than breast cancer. • 卵巢癌比乳腺癌罕见得多。

• Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking oestrogen-only or combined oestrogen-progestogen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping. • 来自大型荟萃分析的

流行病学证据表明，女性服用纯雌激素或雌激素-孕激素联合 HRT 的风险略有增加，这种风险在使用 5 年内变得明显，并在停止后随着时间的推移而降低。

• Some other studies including the WHI trial suggest that the use of combined HRTs may be associated with a similar, or slightly smaller, risk (see Section 4.8).• 包括 WHI 试验在内的其他一些研究表明，联合 HRT 的使用可能与相似或稍小的风险相关（见第 4.8 节）。

Venous thromboembolism 静脉血栓栓塞

• HRT is associated with a 1.3- to 3-fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later (see Section 4.8).• HRT 与 1.3 至 3 倍发生静脉血栓栓塞 (VTE) 的风险相关，即深静脉血栓形成或肺栓塞。在 HRT 的第一年比以后更可能发生这种事件（参见第 4.8 节）。

• Generally recognised risk factors for VTE include use of oestrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30kg/m2), pregnancy/post-partum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the possible role of varicose veins in VTE. As in all postoperative patients, prophylactic measures need be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery temporarily stopping HRT 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.• 一般公认的 VTE 危险因素包括使用雌激素、年龄较大、大手术、长时间制动、肥胖（BMI > 30kg/m2）、怀孕/产后、系统性红斑狼疮 (SLE) 和癌症。关于静脉曲张在 VTE 中的可能作用尚未达成共识。与所有术后患者一样，需要考虑采取预防措施来预防术后 VTE。如果在择期手术后长期制动，建议提前 4 至 6 周暂时停止 HRT。在妇女完全活动之前，不应重新开始治疗。

• Patients with known thromboembolic states have an increased risk of VTE. HRT may add to this risk. HRT is therefore contraindicated in these patients (see Section 4.3). • 已知血栓栓塞状态的患者发生 VTE 的风险增加。 HRT 可能会增加这种风险。因此，这些患者禁用 HRT（见第 4.3 节）。

• In women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening). If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is 'severe' (e.g. antithrombin, protein S, or protein C deficiencies or a combination of defects) HRT is contraindicated. • 在没有 VTE 个人病史但有一级亲属在年轻时有血栓病史的女性中，可以在仔细咨询其局限性后进行筛查（仅通过筛查发现一部分易血栓缺陷）。如果发现与家庭成员血栓形成分离的易血栓缺陷或如果缺陷是“严重的”（例如抗凝血酶、蛋白 S 或蛋白 C 缺陷或缺陷的组合），则禁用 HRT。

• Those women already on anti-coagulant treatment require careful consideration of the benefit-risk of use of HRT. • 那些已经接受抗凝治疗的女性需要仔细考虑使用 HRT 的收益风险。

• If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea). • 如果在开始治疗后出现 VTE，则应停药。当患者发现潜在的血栓栓塞症状（例如腿部疼痛肿胀、胸部突然疼痛、呼吸困难）时，应告知他们立即联系医生。

Coronary artery disease (CAD) 冠状动脉疾病 (CAD)

• There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-progestogen or oestrogen-only HRT. • 没有来自随机对照试验的证据表明在接受雌激素-孕激素或仅雌激素 HRT 的有或没有现有 CAD 的女性中对心肌梗死有保护作用。

Combined oestrogen-progestogen therapy雌孕激素联合治疗

The relative risk of CAD during use of combined oestrogen-progestogen HRT is slightly increased. As the baseline absolute risk of CAD is strongly dependent on age, the number of extra cases of CAD due to oestrogen-progestogen use is very low in healthy women close to menopause, but will rise with more advanced age. 使用雌孕激素联合 HRT 期间 CAD 的相对风险略有增加。由于 CAD 的基线绝对风险很大程度上取决于年龄，在接近绝经的健康女性中，由于使用雌激素-孕激素而导致的额外 CAD 病例数量非常低，但随着年龄的增长会增加。

Oestrogen-only 仅雌激素

Randomised controlled data found no increased risk of CAD in hysterectomised women using oestrogen-only therapy. 随机对照数据发现，仅使用雌激素治疗的子宫切除妇女患 CAD 的风险没有增加。

Ischaemic stroke 缺血性中风

Combined oestrogen-progestogen and oestrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see Section 4.8). 雌激素-孕激素和仅雌激素联合治疗与缺血性卒中风险增加高达 1.5 倍相关。自绝经以来，相对风险不随年龄或时间而变化。然而，由于中风的基线风险强烈依赖于年龄，使用 HRT 的女性中风的总体风险将随着年龄的增长而增加（见第 4.8 节）。

Hepatitis C 丙型肝炎

During clinical trials with the hepatitis C virus (HCV) combination regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as CHCs (combined hormonal contraceptives). Additionally, also in patients treated with glecaprevir/pibrentasvir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs. Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, had a rate of ALT elevation similar to those not receiving any oestrogens;

however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the regimen glecaprevir/pibrentasvir. See section 4.5. 在丙型肝炎病毒 (HCV) 联合方案 ombitasvir/paritaprevir/ritonavir 联合或不联合达沙布韦的临床试验中，使用含炔雌醇药物的女性，ALT 升高超过正常上限 (ULN) 5 倍的情况显着增加。作为 CHCs（复方激素避孕药）。此外，在使用 glecaprevir/pibrentasvir 治疗的患者中，在使用含炔雌醇药物（如 CHCs）的女性中观察到 ALT 升高。使用含有除炔雌醇以外的雌激素药物（如雌二醇）的女性，其 ALT 升高率与未服用任何雌激素的女性相似；然而，由于服用这些其他雌激素的女性人数有限，因此需要谨慎与联合用药方案 ombitasvir/paritaprevir/ritonavir 联合或不联合 dasabuvir 以及 glecaprevir/pibrentasvir 方案共同给药。请参阅第 4.5 节。

Other conditions 其他条件

• Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.. • 雌激素可能导致体液潴留，因此应仔细观察心脏或肾功能不全的患者。

• Women with pre-existing hypertriglyceridaemia should be followed closely during oestrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition. • 在雌激素替代治疗或激素替代治疗期间，应密切关注既往存在高甘油三酯血症的女性，因为在这种情况下使用雌激素治疗会导致血浆甘油三酯大量增加导致胰腺炎的罕见病例。

• Oestrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum i.e. corticoid binding globulin (CBG), sex-hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biological active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-I-antitrypsin, ceruloplasmin). • 雌激素增加甲状腺结合球蛋白 (TBG)，导致循环总甲状腺激素增加，这是通过蛋白质结合碘 (PBI)、T4 水平（通过柱或通过放射免疫测定法）或 T3 水平（通过放射免疫测定法）测量的。 T3 树脂吸收减少，反映 TBG 升高。游离 T4 和游离 T3 浓度不变。血清中的其他结合蛋白可能升高，即皮质类固醇结合球蛋白 (CBG)、性激素结合球蛋白 (SHBG)，分别导致循环皮质类固醇和性类固醇的增加。游离或生物活性激素浓度不变。其他血浆蛋白可能增加（血管紧张素原/肾素底物、α-I-抗胰蛋白酶、铜蓝蛋白）。

• Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should minimise exposure to the sun or ultraviolet radiation whilst taking HRT.• 偶尔会出现黄褐斑，尤其是有妊娠黄褐斑病史的女性。有黄褐斑倾向的女性在服用 HRT 时应尽量减少日晒或紫外线辐射。

• HRT use does not improve cognitive function. There is some evidence of increased risk of probable dementia in women who start using continuous combined or oestrogen-only HRT after the age of 65.• HRT 的使用不会改善认知功能。有一些证据表明，在 65 岁之后开始使用持续联合或仅雌激素 HRT 的女性患痴呆症的风险增加。

• Progynova is not suitable as a contraceptive. If appropriate, contraception should be practised with non-hormonal methods. • Progynova 不适合作为避孕药。如果合适，应使用非激素方法进行避孕。

• Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.• 患有果糖不耐受、葡萄糖-半乳糖吸收不良或蔗糖-异麦芽糖酶不足等罕见遗传问题的患者不应服用该药。

• Patients with rare hereditary problems of galactose intolerance, the Lapp lactasedeficiency or glucose-galactose malabsorption should not take this medicine.• 患有罕见遗传性半乳糖不耐症、拉普乳糖酶缺乏症或葡萄糖-半乳糖吸收不良的患者不应服用该药。

• Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema. • 外源性雌激素可能诱发或加重遗传性和获得性血管性水肿的症状。

4.5 Interaction with other medicinal products and other forms of interaction 与其他药品的相互作用和其他形式的相互作用

Note: The prescribing information of concomitant medication should be consulted to identify potential interactions. 注意：应查阅伴随药物的处方信息以确定潜在的相互作用。

Effects of other medicinal products on Progynova 其他药物对 Progynova 的影响

Substances increasing the clearance of sex hormones (diminished efficacy by enzyme-induction), e.g.: 增加性激素清除率的物质（通过酶诱导降低功效），例如：

The metabolism of oestrogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. barbiturates, phenytoin, primidone, carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz) and possibly also felbamate, griseofulvin, oxcarbazepine, topiramate and products containing the herbal remedy St. John's Wort (Hypericum perforatum). 雌激素的代谢可以通过同时使用已知诱导药物代谢酶的物质来增加，特别是细胞色素 P450 酶，如抗惊厥药（如巴比妥类、苯妥英、扑米酮、卡马西平）和抗感染药（如利福平、利福布丁、奈韦拉平、依法韦仑），可能还有非尔氨酯、灰黄霉素、奥卡西平、托吡酯和含有草药圣约翰草（贯叶连翘）的产品。

Clinically, an increased metabolism of oestrogens and progestogens may lead to decreased effect and changes in the uterine bleeding profile. 临床上，雌激素和孕激素的代谢增加可能导致效果降低和子宫出血特征的变化。

Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After cessation of drug therapy enzyme

induction may be sustained for about 4 weeks. 治疗几天后已经可以观察到酶诱导。最大酶诱导通常在几周内出现。药物治疗停止后，酶诱导可能会持续约 4 周。

Substances with variable effects on the clearance of sex hormones: 对性激素清除有不同影响的物质：

When co-administered with sex hormones, many combinations of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors including combinations with HCV inhibitors, can increase or decrease plasma concentrations of oestrogen. The net effect of these changes may be clinically relevant in some cases. 当与性激素共同给药时，HIV 蛋白酶抑制剂和非核苷类逆转录酶抑制剂的许多组合，包括与 HCV 抑制剂的组合，可以增加或降低雌激素的血浆浓度。在某些情况下，这些变化的净效应可能与临床相关。

Therefore, the prescribing information of concomitant HIV/HCV medications should be consulted to identify potential interactions and any related recommendations. 因此，应查阅伴随 HIV/HCV 药物的处方信息，以确定潜在的相互作用和任何相关建议。

Substances decreasing the clearance of sex hormones (enzyme inhibitors): 降低性激素清除率的物质（酶抑制剂）：

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. fluconazole, itraconazole, ketoconazole, voriconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the oestrogen. 唑类抗真菌药（如氟康唑、伊曲康唑、酮康唑、伏立康唑）、维拉帕米、大环内酯类（如克拉霉素、红霉素）、地尔硫卓和葡萄柚汁等强和中度 CYP3A4 抑制剂可增加雌激素的血浆浓度。

Other interactions 其他互动

During clinical trials with the HCV combination drug regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as CHCs. Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the regimen with glecaprevir/pibrentasvir (see section 4.4). 在 HCV 联合药物方案 ombitasvir/paritaprevir/ritonavir 联合或不联合达沙布韦的临床试验中，使用含炔雌醇药物（如 CHCs）的女性，ALT 升高超过正常上限 (ULN) 5 倍的频率明显更高。使用含有除炔雌醇以外的雌激素药物（如雌二醇）的女性，其 ALT 升高率与未服用任何雌激素的女性相似；然而，由于服用这些其他雌激素的女性人数有限，因此在与联合用药方案 ombitasvir/paritaprevir/ritonavir 联合或不联合达沙布韦以及与 glecaprevir/pibrentasvir 联合用药时需要谨慎（见第 4.4 节）。

Laboratory tests 实验室测试

The use of sex steroids may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins, e.g. corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism, and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range. For more information see section 4.4 “Other conditions”. 性类固醇的使用可能会影响某些实验室测试的结果，包括肝脏、甲状腺、肾上腺和肾功能的生化参数，（载体）蛋白质的血浆水平，例如。皮质类固醇结合球蛋白和脂质/脂蛋白部分、碳水化合物代谢参数以及凝血和纤维蛋白溶解参数。变化通常保持在正常的实验室范围内。如需更多信息，请参阅第 4.4 节“其他条件”。

4.6 Fertility, pregnancy and lactation 生育、妊娠和哺乳

• Pregnancy • 妊娠

Progynova is not indicated during pregnancy. If pregnancy occurs during medication with Progynova treatment should be withdrawn immediately. Progynova 在怀孕期间不适用。 如果在服用 Progynova 治疗期间发生怀孕，应立即停止。

The results of most epidemiological studies to date relevant to inadvertent foetal exposure to oestrogens indicate no teratogenic or foetotoxic effects. 迄今为止，大多数与胎儿无意接触雌激素有关的流行病学研究结果表明，没有致畸或毒性作用。

• Breast-feeding • 母乳喂养

Progynova is not indicated during breast-feeding. Progynova 在母乳喂养期间不适用。

4.7 Effects on ability to drive and use machines 对驾驶和使用机器能力的影响

No studies on the effects on the ability to drive and use machines have been performed. No effects on ability to drive and use machines have been observed in users of Progynova. 尚未进行关于对驾驶和使用机器能力的影响的研究。 在 Progynova 用户中没有观察到对驾驶和使用机器的能力有任何影响。

4.8 Undesirable effects 不良反应

The following undesirable effects have been reported in users of Progynova and other oral HRT preparations. 在 Progynova 和其他口服 HRT 制剂的使用者中报告了以下不良反应。

Neoplasms benign, malignant and unspecified 良性、恶性和未特指的肿瘤

Breast cancer*, Endometrial cancer* 乳腺癌*、子宫内膜癌*

Immune system disorders 免疫系统疾病

Hypersensitivity reaction, Exacerbation of hereditary angioedema 超敏反应、遗传性血管性水肿加重

Metabolism and nutrition disorder 代谢和营养障碍

Porphyria aggravated, Increased or decreased weight, Increased appetite, Carbohydrate tolerance decreased 卟啉症加重，体重增加或减少，食欲增加，碳水化合物耐受性下降

Psychiatric disorders 精神疾病

Anxiety/depressive symptoms, Decreased or increased libido 焦虑/抑郁症状，性欲降低或增加

Nervous system disorders 神经系统疾病

Migraine, Headache, Dizziness, Fatigue, Chorea, Stroke* 偏头痛、头痛、头晕、疲劳、舞蹈病、中风*

Eye disorders 眼疾

Visual disturbances, Intolerance to contact lenses 视力障碍，对隐形眼镜不耐受

Cardiac disorders 心脏疾病

Palpitations, Myocardial infarction* 心悸、心肌梗塞*

Vascular disorders 血管疾病

Hypertension, Thrombophlebitis, Venous Thromboembolism* 高血压、血栓性静脉炎、静脉血栓栓塞*

Respiratory, thoracic and mediastinal disorders 呼吸、胸和纵隔疾病

Epistaxis 鼻出血

Gastrointestinal disorders 胃肠道疾病

Dyspepsia, Abdominal pain, Vomiting, Nausea, Bloating, Flatulence 消化不良、腹痛、呕吐、恶心、腹胀、胀气

Hepatobiliary disorders 肝胆疾病

Gall bladder disease including Cholestasis 胆囊疾病，包括胆汁淤积

Skin and subcutaneous tissue disorders 皮肤和皮下组织疾病

Rashes, various Skin disorders (including Pruritus, Eczema, Urticaria, Acne, Hirsutism, Hair loss, Erythema nodosum, Erythema multiforme, Rash hemorrhagic, Chloasma (see section 4.4) 皮疹、各种皮肤病（包括瘙痒、湿疹、荨麻疹、痤疮、多毛症、脱发、结节性红斑、多形性红斑、出血性皮疹、黄褐斑（见第 4.4 节）

Musculoskeletal and connective tissue disorders 肌肉骨骼和结缔组织疾病

Muscle cramps, Leg pain 肌肉痉挛，腿痛

Renal and urinary disorders 肾脏和泌尿系统疾病

Cystitis-like symptom 膀胱炎样症状

Reproductive system and breast disorders 生殖系统和乳腺疾病

Increased size of uterine fibroids, Vaginal candidosis, Uterine cervical erosions, Changes in vaginal bleeding pattern and abnormal bleeding or flow, Breakthrough bleeding, Spotting (bleeding irregularities usually subside during continued treatment), Dysmenorrhoea, Changes in vaginal secretion, Premenstrual-like syndrome, Breast secretion, Breast tenderness, enlargement or pain.子宫肌瘤增大，阴道念珠菌病，子宫颈糜烂，阴道出血模式改变和异常出血或流量，穿透性出血，血斑（出血不规则通常在继续治疗期间消退），痛经，阴道分泌物变化，经前样综合征，乳房分泌物、乳房压痛、肿大或疼痛。

General disorders and administration site conditions一般疾病和给药部位条件

Oedema 浮肿

* Please see further information below. * 请参阅下面的更多信息。

Breast cancer risk 乳腺癌风险

• An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestogen therapy for more than 5 years. • 据报道，接受雌激素-孕激素联合治疗超过 5 年的女性患乳腺癌的风险增加了 2 倍。

• The increased risk in users of oestrogen-only therapy is lower than that seen in users of oestrogen-progestogen combinations.• 仅使用雌激素治疗的使用者增加的风险低于使用雌激素-孕激素组合的使用者。

• The level of risk is dependent on the duration of use (see section 4.4). • 风险等级取决于使用时间（参见第 4.4 节）。

• Absolute risk estimations based on results of the largest randomised placebo-controlled trial (WHI study) and the largest meta-analysis of prospective epidemiological studies are presented. • 提供了基于最大的随机安慰剂对照试验（WHI 研究）和最大的前瞻性流行病学研究荟萃分析结果的绝对风险估计。

Largest meta-analysis of prospective epidemiological studies – Estimated additional risk of breast cancer after 5 years' use in women with BMI 27 (kg/m2) 前瞻性流行病学研究的最大荟萃分析——估计 BMI 27 (kg/m2) 女性使用 5 年后患乳腺癌的额外风险

Age at start HRT (years) 开始 HRT 年龄	Incidence per 1000 never-users of HRT over a 5 year period (50-54 years)a 5 年内每 1000 名从未使用过 HRT 的人的发病率	Risk ratio 风险比	Additional cases per 1000 HRTusers after 5 years 5 年后每 1000 名 HRT 用户的额外病例数
Oestrogen-only HRT 仅雌激素 HRT			
50	13.3	1.2	2.7

Combined oestrogen-progestogen 雌孕激素联合			
50	13.3	1.6	8.0
a Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m2). a 取自 2015 年英格兰 BMI 27 (kg/m2) 女性的基线发病率。 Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately. 注：由于乳腺癌的背景发病率因欧盟国家而异，新增乳腺癌病例的数量也会相应变化。			

Estimated additional risk of breast cancer after 10 years' use in women with BMI 27 (kg/m2)
在 BMI 27 (kg/m2) 的女性中使用 10 年后估计的额外乳腺癌风险

Age at start HRT (years) 开始 HRT 年龄	Incidence per 1000 never-users of HRT over a 10 year period (50-59 years)a 10 年内每 1000 名从未使用过 HRT 的人的发病率	Risk ratio 风险比	Additional cases per 1000 HRTusers after 1- years 10 年后每 1000 名 HRT 用户的额外病例数
Oestrogen only HRT 仅雌激素 HRT			
50	26.6	1.3	7.1
Combined oestrogen-progestogen 雌孕激素联合			
50	26.6	1.8	20.8
*Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m2) *取自 2015 年英格兰 BMI 27 (kg/m2) 女性的基线发病率 Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately. 注：由于乳腺癌的背景发病率因欧盟国家而异，新增乳腺癌病例的数量也会相应变化。			

US WHI studies - additional risk of breast cancer after 5 years of use

美国 WHI 研究 - 使用 5 年后患乳腺癌的额外风险

WHI: 女性健康倡议

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95% CI	Additional cases per 1000 HRT users over 5 years (95% CI)

年龄范围	5 年内安慰剂组每 1000 名女性的发病率	风险比和 95% CI CI: I-置信区间	5 年内每 1000 名 HRT 用户的额外病例数 (95% CI)
CEE oestrogen-only 仅 CEE 雌激素 CEE:结合性激素			
50 - 79	21	0.8 (0.7 – 1.0)	-4 (-6 - 0) a
CEE + MPA oestrogen & progestogen b CEE + MPA 雌激素和孕激素 B CEE:结合性激素,MPA：加醋酸甲羟孕酮			
50 - 79	17	1.2 (1.0 – 1.5)	+4 (0 - 9)
a WHI study in women with no uterus, which did not show an increased in risk of breast cancer. A 在没有子宫的女性中进行的 WHI 研究表明，患乳腺癌的风险并未增加。 b When the analysis was restricted to women who had not used HRT prior to the study there was no increased risk apparent during the first 5 years of treatment: after 5 years the risk was higher than in non-users. B 当分析仅限于在研究前未使用过 HRT 的女性时，在治疗的前 5 年内风险没有明显增加：5 年后风险高于未使用 HRT 的女性。			

Endometrial cancer risk子宫内膜癌风险

Postmenopausal women with a uterus　　有子宫的绝经后妇女

The endometrial cancer risk is about 5 in every 1000 women with an uterus not using HRT.
子宫内膜癌风险约为每 1000 名未使用 HRT 的子宫女性中的 5 名。

In women with a uterus, use of oestrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see section 4.4).　　对于有子宫的女性，不推荐使用仅使用雌激素的 HRT，因为它会增加患子宫内膜癌的风险（见第 4.4 节）。

Depending on the duration of oestrogen-only use and oestrogen dose, the increase in risk of endometrial cancer in epidemiology studies varied from between 5 and 55 extra cases diagnosed in every 1000 women between the ages of 50 and 65. 根据仅使用雌激素的持续时间和雌激素剂量，流行病学研究中子宫内膜癌风险的增加在每 1000 名 50 至 65 岁的女性中被诊断出 5 至 55 例额外病例不等。

Adding a progestogen to oestrogen-only therapy for at least 12 days per cycle can prevent this increased risk. In the Million Women Study the use of five years of combined (sequential

or continuous) HRT did not increase risk of endometrial cancer (RR of 1.0 (0.8-1.2)). 每个周期至少 12 天在仅使用雌激素的治疗中添加孕激素可以防止这种风险增加。在百万妇女研究中，使用五年联合（连续或连续）HRT 并未增加子宫内膜癌的风险（RR 为 1.0 (0.8-1.2)）。

Ovarian cancer 卵巢癌

Use of estrogen-only or combined estrogen-progestogen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed diagnosed (see Section 4.4). A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period. 仅使用雌激素或雌激素-孕激素联合 HRT 与诊断卵巢癌的风险略有增加有关（见第 4.4 节）。一项来自 52 项流行病学研究的荟萃分析报告说，与从未使用过 HRT 的女性相比，目前使用 HRT 的女性患卵巢癌的风险增加（RR 1.43，95% CI 1.31-1.56）。对于接受 5 年 HRT 的 50 至 54 岁的女性，这导致每 2000 名用户增加约 1 例。在 50 至 54 岁未服用 HRT 的女性中，2000 年约有 2 名女性将在 5 年内被诊断出患有卵巢癌。

Risk of venous thromboembolism 静脉血栓栓塞的风险

HRT is associated with a 1.3 - 3-fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HT (see section 4.4). Results of the WHI studies are presented: HRT 与发生静脉血栓栓塞 (VTE)（即深静脉血栓形成或肺栓塞）的相对风险增加 1.3 - 3 倍相关。在使用 HT 的第一年更有可能发生此类事件（参见第 4.4 节）。 WHI 研究结果如下：

WHI Studies - additional risk of VTE over 5 years of use WHI 研究 - 使用 5 年以上 VTE 的额外风险

Age range (years) 年龄范围	Incidence per 1000 women in placebo arm over 5 years 5 年内安慰剂组每 1000 名女性的发病率	Risk ratio & 95% CI 风险比和 95% CI	Additional cases per 1000 HRT users 每 1000 名 HRT 用户的额外病例数
Oral oestrogen-only a 口服雌激素 A			
50 - 59	7	1.2 (0.6 – 2.4)	1 (-3 - 10)
Oral combined oestrogen & progestogen b 口服联合雌孕激素 B			

50 - 59	4	2.3 (1.2 – 4.3)	5 (1 - 13)
a Study in women with no uterus. A 在没有子宫的女性中进行的一项研究。 ?注释 B 呢怎么没有			

Risk of coronary artery disease 冠状动脉疾病的风险

The risk of coronary artery disease is slightly increased in users of combined oestrogen-progestogen HRT over the age of 60 (see section 4.4). 60 岁以上使用雌孕激素联合 HRT 的患者患冠状动脉疾病的风险略有增加（见第 4.4 节）。

Risk of ischaemic stroke 缺血性中风的风险

The use of oestrogen-only and oestrogen-progestogen therapy is associated with an up to 1.5-fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT. 仅使用雌激素和雌激素-孕激素治疗与缺血性卒中的相对风险增加高达 1.5 倍有关。 使用 HRT 不会增加出血性中风的风险。

This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age dependent, the overall risk of stroke in women who use HRT will increase with age, see section 4.4. 这种相对风险不取决于年龄或使用持续时间，但由于基线风险强烈依赖于年龄，因此使用 HRT 的女性中风的总体风险将随着年龄的增长而增加，见第 4.4 节。

WHI studies combined - Additional risk of ischaemic strokea over 5 years of use WHI 研究相结合 - 使用 5 年以上的缺血性中风的额外风险

Age range (years) 年龄范围	Incidence per 1000 women in placebo arm over 5 years 5 年内安慰剂组每 1000 名女性的发病率	Risk ratio & 95% CI 风险比和 95% CI	Additional cases per 1000 HRT Users over 5 years 5 年内每 1000 名 HRT 用户的额外病例数
50 - 59	8	1.3 (1.1 – 1.6)	3 (1 – 5)

a No differentiation was made between ischaemic and haemorrhagic stroke. A 没有区分缺血性和出血性中风。

Other adverse reactions have been reported in association with oestrogen/progestogen treatment: 其他与雌激素/孕激素治疗相关的不良反应也有报道：

- Gall bladder disease. - 胆囊疾病。

- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura - 皮肤和皮下疾病：黄褐斑、多形性红斑、结节性红斑、血管性紫癜

- Probable dementia over the age of 65 (see section 4.4) - 65 岁以上可能患有痴呆症（见第 4.4 节）

Reporting of suspected adverse reactions 疑似不良反应报告

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard. 在药品批准后报告可疑的不良反应很重要。 它允许持续监测药品的收益/风险平衡。 要求医疗保健专业人员通过黄卡计划报告任何可疑的不良反应，网址为：www.mhra.gov.uk/yellowcard。

4.9 Overdose 过量 服药

Overdose may cause nausea and vomiting and withdrawal bleeding may occur in some women. There are no specific antidotes and treatment should be symptomatic. 过量服药可能导致恶心和呕吐，一些女性可能会出现停药性出血。目前还没有特定的解毒剂，治疗应对症下药

5. Pharmacological properties 药理性质

5.1 Pharmacodynamic properties 药效学特性

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, natural and semisynthetic oestrogens, plain, ATC code: G03CA03 药物治疗组：性激素和生殖系统调节剂，天然和半合成雌激素，普通，ATC 代码：G03CA03

• Estradiol/estradiol valerate: • 雌二醇/戊酸雌二醇：

Progynova contains estradiol valerate, (the valeric-acid ester of the endogenous female oestrogen, estradiol. Progynova 含有戊酸雌二醇，（内源性雌性雌激素，雌二醇的戊酸酯。

The active ingredient estradiol valerate, a prodrug of the synthetic 17ß-estradiol, is chemically and biologically identical to endogenous human estradiol. It substitutes for the loss of oestrogen production in menopausal women, and alleviates menopausal symptoms. Oestrogens prevent bone loss following menopause or ovariectomy. 活性成分戊酸雌二醇是合成 17ß-雌二醇的前药，在化学和生物学上与内源性人体雌二醇相同。它可以替代更年期妇女雌激素产生的损失，并缓解更年期症状。雌激素可防止绝经或卵巢切除术后的骨质流失。

Ovulation is not inhibited during the use of Progynova, and the endogenous production of hormones is hardly affected.使用 Progynova 期间不抑制排卵，几乎不影响内源性激素的产生。

Clinical trial information 临床试验信息

Relief of oestrogen-deficiency symptoms and bleeding patterns 缓解雌激素缺乏症状和出血模式

- During the climacteric, the reduction and finally loss of ovarian estradiol secretion can result in instability of thermoregulation, causing hot flushes associated with sleep disturbance and excessive sweating, and urogenital atrophy with symptoms of vaginal dryness, dyspareunia and urinary incontinence. Less specific but often mentioned as part of the climacteric syndrome are symptoms like anginal complaints, palpitations, irritability, nervousness, lack of

energy and concentration abilities, forgetfulness, loss of libido and joint and muscle pain. HRT alleviates many of these symptoms of estradiol deficiency in the menopausal woman.- 在更年期，卵巢雌二醇分泌减少并最终丧失可导致体温调节不稳定，引起与睡眠障碍和出汗过多有关的潮热，以及伴有阴道干燥、性交困难和尿失禁症状的泌尿生殖道萎缩。作为更年期综合征的一部分，不太具体但经常被提及的是心绞痛、心悸、易怒、紧张、缺乏精力和注意力、健忘、性欲减退以及关节和肌肉疼痛等症状。 HRT 可减轻绝经期妇女雌二醇缺乏的许多症状。

- Relief of menopausal symptoms was achieved during the first few weeks of treatment. - 在治疗的最初几周内实现了更年期症状的缓解。

- The addition of a progestogen to an oestrogen replacement regimen like Progynova for at least 10 days per cycle is recommended in women with an intact uterus. It reduces the risk of endometrial hyperplasia and the attendant risk of adenocarcinoma in these women. The addition of a progestogen to an oestrogen replacement regimen has not been shown to interfere with the efficacy of oestrogen for its approved indications.- 对于子宫完整的女性，建议在 Progynova 等雌激素替代方案中添加孕激素，每个周期至少 10 天。它降低了这些女性子宫内膜增生的风险和随之而来的腺癌风险。没有显示在雌激素替代方案中添加孕激素会干扰雌激素对其批准适应症的功效。

Prevention of osteoporosis 预防骨质疏松症

- Oestrogen deficiency at menopause is associated with an increasing bone turnover and decline in bone mass. - 绝经期雌激素缺乏与骨转换增加和骨量下降有关。

- The effect of oestrogens on the bone mineral density is dose-dependent. Protection appears to be effective for as long as treatment is continued. After discontinuation of HRT, bone mass is lost at a rate similar to that in untreated women. - 雌激素对骨矿物质密度的影响是剂量依赖性的。只要继续治疗，保护似乎就有效。停止 HRT 后，骨量的流失速度与未接受治疗的女性相似。

- Evidence from the WHI trial and meta-analysed trials shows that current use of HRT alone or in combination with a progestogen – given to predominantly healthy women – reduces the risk of hip, vertebral, and other osteoporotic fractures. HRT may also prevent fractures in women with low bone density and/or established osteoporosis, but the evidence for that is limited. - 来自 WHI 试验和荟萃分析试验的证据表明，目前单独使用 HRT 或与孕激素联合使用（主要用于健康女性）可降低髋部、脊椎和其他骨质疏松性骨折的风险。 HRT 还可以预防骨密度低和/或骨质疏松症女性的骨折，但这方面的证据有限。

Observational studies and the WHI trial on conjugated equine oestrogens (CEE) plus medroxyprogesterone acetate (MPA) suggest a reduction of colon cancer morbidity in postmenopausal women taking HRT. In the WHI trial on CEE mono-therapy a risk reduction was not observed. It is unknown whether these findings also extend to other HRT products.

对结合马雌激素 (CEE) 加醋酸甲羟孕酮 (MPA) 的观察性研究和 WHI 试验表明，服用 HRT 可降低绝经后妇女的结肠癌发病率。在 CEE 单一疗法的 WHI 试验中，没有观察到风险降低。尚不清楚这些发现是否也适用于其他 HRT 产品。

• Progestogen: • 孕激素：

As oestrogens promote the growth of the endometrium, unopposed oestrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestogen greatly reduces the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women. 由于雌激素促进子宫内膜的生长，未对抗的雌激素会增加子宫内膜增生和癌症的风险。添加孕激素可大大降低未切除子宫的女性因雌激素引起的子宫内膜增生风险。

5.2 Pharmacokinetic properties 药动学特性

Absorption 吸收

After oral administration estradiol valerate is quickly and completely absorbed. 口服戊酸雌二醇后吸收迅速而完全。

Distribution 分配

Already after 0.5 - 3 hours peak plasma levels of estradiol, the active drug substance, are measured. As a rule, after 6 - 8 hours a second maximum appears, possibly indicating an entero-hepatic circulation of estradiol. 在 0.5-3 小时后，已经测量了活性药物物质雌二醇的血浆峰值水平。通常，在 6-8 小时后出现第二个最大值，这可能表明雌二醇的肠肝循环。

In plasma, estradiol is mainly found in its protein-bound form. About 37% are bound to SHBG and 61% to albumin. Cumulation of estradiol after daily repetitive intake of Progynova does not need to be expected. 在血浆中，雌二醇主要以其蛋白质结合形式存在。约 37% 与 SHBG 结合，61% 与白蛋白结合。不需要预期每天重复摄入 Progynova 后雌二醇的累积。

The absolute bioavailability of estradiol amounts to 3 - 5% of the oral dose of estradiol valerate. 雌二醇的绝对生物利用度为戊酸雌二醇口服剂量的 3-5%。

Biotransformation 生物转化

Esterases in plasma and the liver quickly decompose estradiol valerate into estradiol and valeric acid. Further decomposition of valeric acid through β-oxidation leads to C2-units and results in CO2 and water as end products. Estradiol itself undergoes several hydroxylating steps. Its metabolites as well as the unchanged substance are finally conjugated. Intermediate products of metabolism are estrone and estriol, which exhibit a weak oestrogenic activity of their own, although this activity is not so pronounced as with estradiol. The plasma concentration of conjugated estrone is about 25 to 30 fold higher than the concentration of unconjugated estrone. In a study using radioactive labelled estradiol valerate about 20% of radioactive substances in the plasma could be characterised as unconjugated steroids, 17% as glucuronized steroids and 33% as steroid sulphates. About 30% of all substances could not be extracted from the aqueous phase and, therefore, probably represent metabolites of high polarity. 血浆和肝脏中的酯酶迅速将戊酸雌二醇分解为雌二醇和戊酸。戊酸通过 β 氧化进一步分解产生 C2 单元并产生 CO2 和水作为最终产物。雌二醇本身经历了几个羟基化步骤。其代谢物以及未改变的物质最终被结合。代谢的中间产物是雌酮和雌三醇，它们本身表现出弱的雌激素活性，尽管这种活性不如雌二醇那么明显。结合雌酮的血浆浓度比非结合雌酮的浓度高约 25 至 30 倍。在一项使用放射性标记的戊酸雌二醇的研究

中，血浆中约 20% 的放射性物质可被表征为非结合类固醇，17% 为葡萄糖醛酸化类固醇，33% 为类固醇硫酸盐。大约 30% 的物质不能从水相中萃取出来，因此可能代表高极性的代谢物。

Elimination 代谢

Estradiol and its metabolites are mainly excreted by the kidneys (relation of urine:faeces = 9:1). Within 5 days about 78 - 96% of the administered dose are excreted with an excretion half-life of about 27 hours. 雌二醇及其代谢物主要由肾脏排泄（小便：大便=9：1）。在 5 天内，约 78-96% 的给药剂量被排泄，排泄半衰期约为 27 小时。

5.3 Preclinical safety data 临床前安全数据

There are no preclinical safety data which could be of relevance to the prescriber and which are not already included in other relevant sections of the SPC. 没有可能与处方者相关的临床前安全性数据，这些数据尚未包含在 SPC 的其他相关部分中。

6. Pharmaceutical particulars 药品详情

6.1 List of excipients辅料清单

Lactose monohydrate 单水乳糖

Maize Starch 玉米粉

Povidone 25 聚维酮 25

Talc 滑石粉

Magnesium Stearate [E572] 硬脂酸镁 [E572]

Sucrose 蔗糖

Povidone 90 聚维酮 90

Macrogol 6000 聚乙二醇 6000

Calcium Carbonate [E170] 碳酸钙 [E170]

Glycol montanate 褐煤酸乙二醇酯

Purified Water 净化水

6.2 Incompatibilities 不相容性

None known. 不知道。

6.3 Shelf life 保质期

5 years. 5 年。

6.4 Special precautions for storage储存的特殊注意事项

None. 无。

6.5 Nature and contents of container 容器的性质和内容物

Container consists of aluminium foil and PVC blister strips packed in a cardboard carton 容器由铝箔和 PVC 吸塑条组成，包装在便携纸盒中

Presentation: Carton containing memo-packs of either 1 x 28 tablets or 3 x 28 tablets.介绍：编写纸盒包装内含 1 x 28 片或 3 x 28 片。

6.6 Special precautions for disposal and other handling 处置和其他处理的特殊注意事项

None. 无。

7. Marketing authorisation holder 销售许可持有人

Bayer plc拜耳

400 South Oak Way

Reading, RG2 6AD

8. Marketing authorisation number(s) 销售授权号

PL 00010/0557 PL 00010/0557

9. Date of first authorisation/renewal of the authorisation 首次授权/授权更新日期

1-May-08 2008 年 5 月 1 日

10. Date of revision of the text 文本修改日期

9-Jun-22 2022 年 6 月 9 日